Outcomes of Descemet's membrane endothelial keratoplasty for congenital hereditary endothelial dystrophy

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PURPOSE To report outcomes of Descemet's membrane endothelial keratoplasty (DMEK) in eyes with congenital hereditary endothelial dystrophy (CHED).

METHODS The medical records of patients with CHED who underwent DMEK were retrospectively reviewed. Pre- and postoperative visual acuity, corneal thickness, corneal clarity, and graft survival, were analyzed, and intra- and postoperative complications were assessed.

RESULTS A total of 14 eyes of 8 patients were included. Surgery was performed at a mean age of 10 ± 7 years (range, 2-23). DMEK was successfully performed in all eyes, with 13 of 14 eyes (93%) maintaining a clear cornea at final follow-up (mean, 16.9 ± 8.1 months). Following surgery, corrected distance visual acuity improved from 0.9 ± 0.3 logMAR (Snellen 20/158) to 0.4 ± 0.2 (20/50), and pachymetry improved from 932 ± 57 μm to 642 ± 93 μm. Endothelial cell loss was 33%, and average cell counts were 1767 ± 281 cells/mm^2 at final follow-up. Intraoperative aqueous misdirection occurred in both eyes of a 2-year-old child, requiring pars plana vitrectomy. Postoperative donor Descemet's membrane detachment occurred in 4 eyes. Rebubbling was performed in 3 eyes (21%); 1 eye had spontaneous reattachment. One eye (8%) had possible graft failure during follow-up, requiring repeat DMEK surgery.

CONCLUSIONS In our study cohort of eyes with CHED, DMEK was performed with good visual outcome. Rebubbling was necessary for donor reattachment in the early postoperative period in some cases. (J AAPOS 2020;24:358.e1-6)

Congenital hereditary endothelial dystrophy (CHED) is a rare disorder characterized by congenital or infantile-onset bilateral corneal clouding that causes impaired vision, photophobia, tearing, and nystagmus along with increased risk of amblyopia.[1] Severe corneal edema occurs due to atrophic, dysfunctional endothelium and thickened Descemet's membrane (DM).[2] The course of disease may be relatively stationary, or it progress over time.[3]

CHED has usually been treated with penetrating keratoplasty (PK), although there is no consensus on appropriate timing for PK, because risk of amblyopia must be weighed against increased risk of complications in younger patients.[4,5] Technically, PK is more challenging in children not only because of increased tissue elasticity and the relatively small operating field but also because of higher risk of postoperative complications such as suture-related infections and graft rejection.[6]

Selective replacement of dysfunctional endothelium has been successfully performed in CHED patients, with promising results, using endothelial keratoplasty (EK) techniques, including Descemet's stripping endothelial keratoplasty (DSEK) and Descemet's stripping automated endothelial keratoplasty (DSAEK).[7-10] The advantages of EK include no suture-related complications, faster refractive stability, greater tectonic strength, and reduced graft rejection rates.

Descemet's membrane endothelial keratoplasty (DMEK) allows isolated transfer of healthy donor DM and endothelial cells and could be a good option in cases of CHED because it restores normal corneal anatomy, allows for relatively fast visual recovery, and carries a low risk of endothelial rejection.[12] We report our initial experience using DMEK in eyes with CHED in terms of surgical challenges, postoperative outcomes, and safety. To our knowledge, this is the first case series of DMEK performed in patients, including children, who have CHED.

Subjects and Methods

We retrospectively reviewed the medical records of all patients who underwent DMEK for CHED between January 2017 to

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Submitted May 13, 2020.
Revision accepted July 25, 2020.
Published online November 27, 2020.
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1091-8531/$36.00
https://doi.org/10.1016/j.jaapos.2020.07.018

July 2019 at one of two hospitals, with a single surgeon at each (RF, Apollo Hospitals, Hyderabad, India; AS, Rothschild foundation, Paris, France). This study adhered to the tenets of the Declaration of Helsinki. The diagnosis of CHED was based on clinical findings of bilateral diffuse corneal edema with increased stromal thickness in early childhood, after other possible diagnoses were ruled out. Informed consent for surgery was obtained from all patients or legal guardians. All surgeries were performed under general anesthesia for patients ≤18 years of age and peribulbar anesthesia for older patients (50% mixture of lidocaine 2% and bupivacaine 0.5%).

Suitable donor corneas were obtained from the eye bank (age group, 50-70 years and cell counts of ≥2500/mm^2). Donor DM stripping was performed using a standardized technique, as previously described.[13] The surgical technique for DMEK was similar for both surgeons. Epithelial debridement was performed to improve visualization. A clear corneal incision of 2.2–2.8 mm was combined with 2 or 3 paracenteses. Stripping of DM was not performed in eyes with normal-appearing DM on preoperative anterior segment optical coherence tomography (OCT) evaluation (RTVue, Optovue Inc, Fremont, CA). In some eyes DM removal was performed under cohesive viscoelastic with or without the additional use of an air bubble to improve DM visualization. The area of DM removal was 1 mm larger in diameter than the planned donor graft. Inferior surgical iridectomy was performed in all eyes via limbal paracentesis. Donor DM was inserted into the anterior chamber using a glass injector (Geuder, Heidelberg, Germany) connected to a fluid-filled syringe. The corneal wound was secured with 10-0 nylon suture. A no-touch tapping technique was used to unroll the donor DM, and its correct orientation was confirmed by the F stamp (RF). Intraoperative OCT was also used to assist donor unfolding and confirm right orientation of DM scroll (AS). A bubble (air or 20% sulfur hexafluoride gas) was injected under the graft to fill completely the anterior chamber, maintaining normal intraocular pressure (IOP). A bandage contact lens was placed on the eye, and topical moxifloxacin hydrochloride 0.5% was applied. Videos 1 and 2 (available at jaapos.org) show the surgical technique.

Patients were seen 2 hours after surgery, and IOP was evaluated by finger tension. Patients were examined on postoperative day 1 and thereafter at week 1, month 1, and every 3 months. The need for rebubbling was assessed at each visit, depending on the graft's attachment. If required, the procedure was performed under general anesthesia for patients <18 years of age. Patients were started on topical moxifloxacin hydrochloride 0.5% and 1% prednisolone acetate suspension every 2 hours directly after surgery. Steroid drops were tapered later, depending on resolution of corneal edema over several months. Patients were maintained in a supine position and advised to avoid eye rubbing in the early postoperative period. Visual acuity assessment was made using tumbling E or picture tests for children <5 years of age. Pachymetry was assessed either from anterior segment OCT or using an ultrasonic pachymeter (Tomey SP-100, Nagoya, Japan). Endothelial counts were measured using specular microscopy (Tomey EM-4000, Nagoya, Japan).

Continuous variables were represented as mean and standard deviation. Pre- and postoperative visual acuity were compared using the Wilcoxon signed-rank test. Statistical analyses were performed using Stata V.11.0 statistical software (StataCorp, College Station, TX). A P value of ≤0.05 was considered statistically significant.

Results

A total of 14 eyes of 8 patients were included. Patient characteristics and surgical course are summarized in Table 1. Mean patient age was 10 ± 7 years (range, 2-23). Patients were followed for a mean 16.9 ± 8.1 months (range, 6-30). Mean preoperative corrected distance visual acuity was 0.9 ± 0.3 logMAR. Mean preoperative pachymetry was 933 μm ± 57 μm, (range, 851–1006 μm). DM stripping was performed in 8 cases (57%). Mean donor DM size was 8 mm (range, 7.5–8.5 mm). A sulfur hexafluoride gas bubble was used for tamponade at the end of the procedure in 10 eyes; an air bubble, in 4 eyes of the 2 eldest patients (≥13 years of age). None of the eyes developed pupillary block syndrome because of inferior peripheral iridectomy. IOPs remained within normal parameters through the last follow-up examination.

The cornea cleared well in all eyes following DMEK (Figure 1). Mean postoperative visual acuity was 0.4 ± 0.2 logMAR, with a mean improvement of 0.6 ± 0.3 logMAR (P = 0.001). Mean postoperative pachymetry was 633 ± 120 μm, (range, 539–944 μm). Endothelial cell counts were available for 8 eyes at variable points of follow-up. Mean endothelial cell counts at last follow-up was 1767 ± 281 cells/mm^2 (range, 1320–2247 cells/mm^2), and mean cell loss was 33% (range, 20%-47%). Average donor endothelial cell counts were 2630 ± 99 cells/mm^2 (range, 2543–2814 cells/mm^2).

Intraoperative shallowing of the anterior chamber with raised IOP occurred in both eyes of a 2-year-old child. DM stripping was difficult, requiring greater manipulation over a longer duration. Following inferior peripheral iridectomy and donor insertion, the anterior chamber could not be formed, and the globe became tense, suggestive of possible aqueous misdirection. Intravenous mannitol injection failed to resolve the condition; therefore, pars plana core vitrectomy (25 G) was performed to successfully complete donor unfolding and positioning.

Donor DM detachment occurred in 4 of 14 eyes postoperatively. Rebubbling was successfully performed in 3 of 14 eyes (21%) under general anesthesia at postoperative week one. One eye had a partial DM separation, which resolved spontaneously, with no need for further intervention.

Graft failure with progressive increase in corneal thickness was noted in 1 eye at 5 months' follow-up. Initial resolution of corneal edema and improvement in corrected distance visual acuity of up to 0.6 logMAR was noted at 3 months' follow-up visit. Repeat DMEK was performed successfully.

Table 1. Preoperative and postoperative clinical details of eyes with CHED undergoing DMEK procedure

Case	Sex	Age, years	Eye	DM stripping	Donor size, mm	CDVA, logMAR		Pachymetry, μm		DM detachment/ rebubbling	Follow-up, mos	Donor cornea, cells/mm^2	Specular microscopy post-op cells/mm^2, (follow-up, mos)	Complications
						Before surgery	After surgery	Before surgery	After surgery					
1A	F	2	R	Yes	7.75	1	0.3	NA	730	Yes/Yes	30	NA	NA	intraop aqueous misdirection; post-op donor detachment
1B			L	Yes	7.75	1	0.3	NA	830	Yes/Yes	28	NA	NA	Intra-op aqueous misdirection; post-op donor detachment
2A	F	3	R	No	8	1	0.3	963	638	No	12	2588	NA	
2B			L	No	8	1	0.3	959	619	Yes/Yes	9	2634	NA	Post-op donor detachment
3A	F	7	R	No	8	1.3	0.6	872	548	No	26	2581	1776 (9)	
3B			L	No	8	1	0.3	851	642	No	17	2776	1473 (12)	
4A	M	8	R	No	8	1.3	0.3	864	539	No	25	2814	2247 (12)	
4B			L	No	8	1.3	0.5	861	632	No	17	2628	1808 (12)	
5A	F	10	R	Yes	7.75	0.7	0.5	998	944	No	20	NA	NA	Delayed graft failure
5B			L	Yes	7.5	1	0.8	958	750	No	19	NA	NA	
6	M	13	L	Yes	8	0.6	0.3	1002	730	No	12	2543	1884 (9)	
7	M	16	L	Yes	8.5	1	0.3	1006	587	Partial/no	7	2598	1320 (6)	Post-op partial donor detachment
8A	M	23	R	Yes	8	0.4	0.3	936	553	No	6	2572	1723 (6)	
8B			L	Yes	8	0.6	0.2	924	545	No	9	2669	1908 (9)	

CDVA, corrected distance visual acuity; *DM*, Descemet's membrane.

Discussion

Endothelial keratoplasty techniques such as DSEK and DSAEK have been reported to be successful in eyes with CHED.[8-11] DMEK was unsuccessfully attempted in an infant eye with posterior polymorphous corneal dystrophy.[14] To our knowledge, use of DMEK in CHED patients has not been published previously.

Descemet's stripping is considered an essential step for EK. However, this is often challenging to perform in eyes with CHED because of poor visibility secondary to severe corneal edema and tighter adhesion of DM in younger eyes. Several surgeons have reported intraoperative failure of DM stripping.[8,15,16] Pineda and colleagues[15] reported one of the first cases of attempted DSAEK in a 7-year-old child with CHED that was converted to PK because of the difficulties visualizing and stripping the DM. Non–Descemet's stripping DSAEK has shown good outcomes in eyes after failed PK or with bullous keratopathy.[17] DSEK and DSAEK have also been successfully performed in CHED without removal of host DM.[8,18] Busin and colleagues[8] reported no stripping of DM in infants under 1 year of age because of the same technical difficulties. The authors reported achieving corneal clarity in these infants within 1 week of DSAEK. Ashar and colleagues[18] reported a small case series of older children (mean age, 3 years) who underwent DSAEK for CHED without DM removal and found similar outcomes in terms of visual acuity and corneal clarity compared to DSAEK with DM stripping in this age group. In our study, one surgeon (AS) removed DM in all cases (4 eyes) using a modified technique. Anterior chamber was partially filled with cohesive viscoelastic followed by placement of a midsized air bubble. Viscoelastic maintained the anterior chamber depth and air bubble helped visualization of DM as it was being stripped (Video 3, available at jaapos.org). One surgeon (RF) chose to remove DM only in patients >10 years of age, based on anterior segment OCT appearance of thickened host DM (Figure 2). Omission of DM stripping had two benefits; first, it reduced intraocular surgical manipulations; second, it shortened the duration of surgery.

To strip DM in younger CHED eyes requires greater effort than conventional EK surgery. In addition to the risk of repeated anterior chamber collapse and lens damage, continuous irrigation and manipulation could lead to increased vitreous hydration via inferior paracentesis and induce a high positive vitreous pressure with shallow anterior chamber. This occurred during surgery in both eyes of a 2-year-old child and necessitated a core vitrectomy to resolve the aqueous misdirection (Videos 4 and 5, available at jaapos.org). In view of the increased risk of complications with DM stripping in younger eyes, it may be better to avoid this step in pediatric eyes with CHED if DM appears normal on anterior segment OCT.

Owing to technical difficulties of PK and the high risk of postoperative complications that occur in pediatric eyes (astigmatism, rejection, inflammation), many surgeons

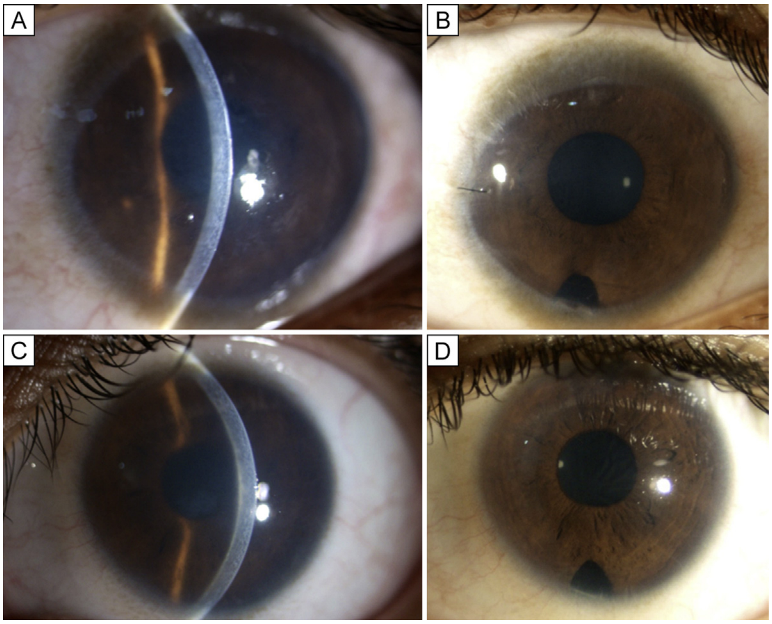

FIG 1. Pre- (A,C) and postoperative (B,D) slit-lamp clinical photographs of 2 cases (case 4A, above; case 8B, below) of congenital hereditary endothelial dystrophy (CHED) cases undergoing Descemet's membrane endothelial keratoplasty (DMEK).

opt to wait on CHED surgery until the risk of amblyopia outweighs the risk of surgical complications. Because endothelial transplants do not risk these complications, it has been suggested that they could be appropriate for younger patients.[8-11] In our series, the mean postoperative corrected distance visual acuity was 0.4 ± 0.2 logMAR, with significant improvement compared to preoperative visual acuity of 0.9 ± 0.3 logMAR (P = 0.001). Comparative visual outcomes between patients <10 years of age versus those ≥10 years of age failed to reveal any difference, with postoperative mean visual acuity of 0.36 ± 0.1 and 0.39 ± 0.2 logMAR, respectively. Corneal thickness decreased significantly in all eyes postoperatively (mean pre- vs postoperative

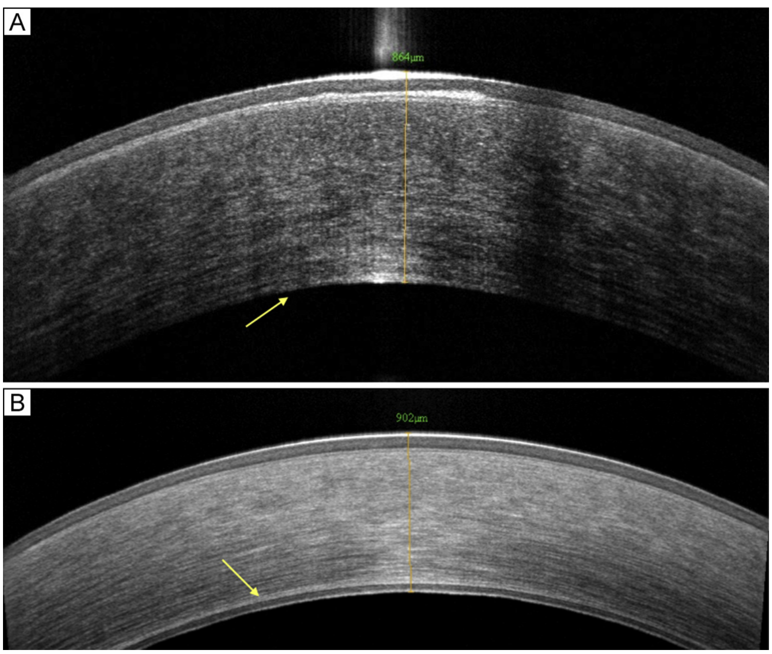

FIG 2. Preoperative anterior segment optical coherence tomography images in eyes with CHED. A, Corneal scan of case 3 showing normal Descemet's membrane (arrow). B, Corneal scan of case 8 showing thickened Descemet's membrane (arrow).

pachymetry, 933 ± 58 vs 633 ± 120 μm [$P = 0.001$]). After DMEK, the stromal collagen fibers appeared more compact on anterior segment OCT, with reduction in corneal pachymetry, restoring normal corneal anatomy.

Of the 14 eyes in our series, 10 (71%) had visual acuity of 20/40 or better across all ages. Our results correlate with the findings of Busin and colleagues,[8] who reported similar outcomes of 20/40 or better in 8 of 9 cases of older children, indicating that CHED may be less amblyogenic compared with other corneal pathologies.

Three eyes (21%) of 2 patients (2 and 3 years of age) in our series required rebubbling for donor detachment 1 week after DMEK. Host DM was removed in 2 eyes and retained in 1 eye. It is possible that DM detachment in these eyes, could be related to eye rubbing or failure to maintain supine position postoperatively rather than to the surgery itself. DM stripping was not performed in 6 eyes of patients <10 years of age (RF), and 20% sulfur hexafluoride was used tamponade in these eyes. Only 1 eye had donor DM detachment, which was successfully managed by rebubbling. Busin and colleagues[8] have reported donor dislocation requiring repeat air injection in 4 of 6 eyes of children <1 year of age, wherein host DM was retained. Lower rebubbling rates have been reported with use of 20% sulfur hexafluoride gas for tamponade instead of 100% air, with comparative long-term visual outcome and endothelial cell loss.[19] Lower detachment rates in our series, where host DM was retained, could be related to the use of 20% sulfur hexafluoride gas for tamponade instead of air. Inferior peripheral iridectomy was performed in all eyes in our series, and none developed pupillary block or raised IOP. Based on our results, 20% sulfur hexafluoride gas may be advisable for anterior chamber fill in pediatric eyes undergoing DMEK for CHED. Performing EK in phakic eyes carries the risk of lenticular changes from surgical manipulation, or postoperative steroid therapy. Incidence of post DSAEK cataract in adults has been reported between 7% and 37%.[20] The crystalline lens remained clear in all eyes in our series at final follow-up; however, longer follow up is required to assess any future lenticular changes and need for intervention.

Endothelial cell loss following DSAEK for CHED ranges from 30% to 50.9%, depending on the duration of follow-up.[8-10] Average endothelial cell loss at 6 months after routine DMEK ranges from 25% to 47%.[12] In our series average endothelial cell loss was 33% at follow-up of 16.9 ± 8.1 months. Our data shows that endothelial cell loss following DMEK is comparable to that following DSAEK in CHED.

The current literature reports that endothelial rejection rates after DMEK range from 1% to 3% and are significantly lower compared with DSAEK.[12] In our series, 93% of cases (13/14) maintained a clear cornea through final follow-up; 1 eye that initially improved at 3 months had corneal edema at 5 months' follow-up, possibly secondary to graft failure from increased endothelial cell loss or an undetected graft rejection. With lower endothelial rejection rates, it is likely that the graft survival after DMEK will be significantly better than after PK or DSAEK in CHED. Because of the lower risk of rejection with DMEK, less aggressive topical medications can also reduce the risk of steroid-induced lenticular changes as well.

Our study is limited by its retrospective design. Additionally, follow-up data were not available at uniform time points. Endothelial imaging data were also not available for all eyes. Despite these limitations, our study shows that DMEK can be performed safely in eyes with CHED and provides good visual outcomes with few postoperative complications. Retaining host DM in younger eyes does not seem to affect clinical outcome and can help simplify DMEK procedure. DMEK grafts are likely to survive longer due to lower rejection rates; however, studies with longer follow-up are necessary.

Literature Search

PubMed was searched on July 10, 2020, without date or language restriction, using the following terms and combinations: *congenital hereditary endothelial dystrophy*, *CHED*, *congenital endothelial dystrophy and keratoplasty*, *endothelial keratoplasty*, *DSEK*, *DSAEK*, and DMEK.

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